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Infertility treatment associated with childhood asthma and atopy

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STUDY QUESTION: Are children who were conceived with infertility treatment at an increased risk of developing asthma and atopic conditions?

SUMMARY ANSWER: Infertility treatment is associated with an elevated risk of asthma and atopic conditions in early and middle childhood, even after adjustment for parental asthma and atopy.

WHAT IS KNOWN ALREADY: Asthma and atopic conditions are prevalent in childhood. The development of these conditions may be linked to early life exposures, including the use of infertility treatments.

STUDY DESIGN, SIZE, DURATION: Upstate KIDS is a prospective cohort study of singletons and multiples born between 2008 and 2010. A total of 5034 mothers and 6171 children were enrolled and followed up until 2019, and 2056 children participated in the middle childhood follow-up.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Women reported the fertility agents used to become pregnant on a baseline questionnaire. Treatment was categorized as ART (~22%) use, ovulation induction via oral/injectable medications with or without IUI (OI/IUI, ~20%), or no treatment (~58%). Outcomes were assessed by maternal report on questionnaires in early (up to age 3 years, prevalence 9–28%) and middle (7–9 years, prevalence 10–16%) childhood. Weighted Poisson regression models with robust standard errors were used to analyze the risk of atopic outcomes in relation to infertility treatment exposure.

MAIN RESULTS AND THE ROLE OF CHANCE: Compared to children conceived without treatment, children conceived with any infertility treatment were at an increased risk of persistent wheeze by age 3 years (relative risk (RR): 1.66; 95% CI: 1.17, 2.33) with adjustments for parental atopy among other risk factors. Around 7–9 years, children conceived with treatment were more likely to have current asthma (RR: 1.30; 95% CI: 0.98, 1.71), eczema (RR: 1.77; 95% CI: 1.25, 2.49) or be prescribed allergy-related medications (RR: 1.45; 95% CI: 1.06, 1.99). Similar effect sizes were found when examining associations by treatment type (i.e. ART versus OI/IUI).

LIMITATIONS, REASONS FOR CAUTION: Childhood outcomes were based on maternal report and are subject to potential misclassification. There was attrition in this study, which limits the precision of our measures of association.

WIDER IMPLICATIONS OF THE FINDINGS: Though future research is needed to clarify the mechanisms involved, our findings support that both ART and OI/IUI influences the development of asthma and atopic conditions in the offspring from an early age.

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Introduction

Asthma and other atopic diseases are the leading chronic pediatric diseases, affecting around 15% of US children and representing a substantial burden for pediatric health and the healthcare system (Shaw *et al.*, 2011; Weidinger and Novak, 2016; CDC, 2018; Ferrante and La Grutta, 2018; McKenzie and Silverberg, 2019). Risk factors for asthma and other atopic diseases are complex and include genetic as well as environmental factors. Early life exposures including (but not limited to) maternal diet (Best *et al.*, 2016) and phthalate exposure (Gascon *et al.*, 2015) during pregnancy, cesarean delivery (Adeyeye *et al.*, 2019), and preterm delivery (Sonnenschein-van der Voort *et al.*, 2014) have all been implicated in the development of atopic disorders. A systematic review (Kettner et al., 2015) and meta-analysis (Tsabouri *et al.*, 2021) expanded the list of potential early life risk factors for asthma to include infertility and ART. However, associations appear to be sensitive to outcome definitions, plurality, and age at outcome ascertainment (Carson *et al.*, 2013; Tsabouri *et al.*, 2021). Prior studies also lack sufficient data on associations for non-ART types of infertility treatment (Tsabouri *et al.*, 2021). Further, almost no studies have been conducted in the USA, which experiences differences in infertility treatment outcomes (e.g. high ART live birth rates, a lower proportion of singleton pregnancies but higher rates of low birthweight in singletons pregnancies) compared to other countries, potentially owing to differences in the number of embryos transferred per cycle (De Geyter *et al.*, 2020) and other practices (Kushnir *et al.*, 2017), along with access to services. Given these limitations to the literature, evidence of an association between infertility treatment and asthma/atopy is equivocal.

The mechanisms linking infertility treatment and subsequent asthma and atopic outcomes are unknown. Prior work suggests this association is independent of and not mediated by pregnancy outcomes such as pre-eclampsia, preterm delivery, low birthweight, or cesarean delivery (Carson *et al.*, 2013; Kuiper *et al.*, 2015, 2019; Magnus *et al.*, 2019). However, this association may be confounded by inherited immunological disorders, which increases risk of both infertility and childhood asthma/atopy. Though evidence is conflicting, women with asthma and other atopic diseases may be more likely to experience infertility (Juul Gade *et al.*, 2014; Bláfoss *et al.*, 2019; Wasilewska and Małgorzewicz, 2019). Few prior studies have examined whether concurrent adjustment for both paternal and maternal asthma and atopy—which may be linked to childhood atopic diseases via genetic and/or developmental programming mechanisms (Dietert, 2011)—explains the association between infertility treatment and childhood atopic outcomes.

The use of ART is increasing in the USA with around 1.9% of infants born in 2017 being conceived by these technologies (Sunderam *et al.*, 2020). Many more infants are conceived by non-ART infertility treatments (Duwe *et al.*, 2010). Thus, it is critically important to understand whether children conceived by infertility treatment may be at a higher risk of adverse health outcomes, such as asthma and other atopic diseases, appropriately accounting for parental history. Therefore, the primary aim of this study is to examine the association of infertility treatment with childhood atopic diseases.

Materials and methods

Study design and population

The Upstate KIDS Study is a prospective cohort study consisting of 6171 infants delivered between 2008 and 2010 in 57 New York State counties, excluding New York City (Buck Louis *et al.*, 2014). The study was designed to examine the impact of infertility treatment on child growth and development. Based on data available on the birth certificate, singleton infants conceived with infertility treatment were frequency matched (3:1) to infants without treatment by perinatal region of birth (Buck Louis *et al.*, 2014). Multiples (e.g. twins, triplets, etc.) were eligible to participate regardless of infertility treatment status and additional recruitment and follow-up procedures, including the validity of this sampling framework, has been described previously (Buck Louis *et al.*, 2014). In total, 5034 mothers and 6171 children enrolled in the study and follow-up of this cohort continued until 2019. Beginning in 2017, 4644 children were invited to clinic visits which included blood draws and lung inflammation assessments. The New York State Department of Health and the University at Albany (State University of New York) institutional review boards approved the study. All parents provided written informed consent and children assented to clinic visits.

Exposure assessment

Mothers reported all medical services or medications used to become pregnant on a baseline questionnaire administered at 4-months postpartum. Infertility treatment was categorized as: ART use (IVF with or without ICSI, assisted hatching, frozen embryo transfer, zygote intrafallopian transfer, gamete intrafallopian transfer, and/or donor eggs or embryos); ovulation induction (OI) via oral or injectable medications with or without IUI; and no treatment. Linkage to the Society for Assisted Reproductive Technology-Clinical Outcome Reporting System (SART-CORS) confirmed that the sensitivity and specificity of maternal report was high (93% and 99%, respectively) (Buck Louis *et al.*, 2015).

Outcome assessment

Infant atopic outcomes of wheeze, eczema/atopic dermatitis, and allergies were reported by mothers on questionnaires at 4, 8, 12, 18, 24, 30 and 36 months of age. Outcomes of interest were defined in keeping with prior literature (Cloutier *et al.*, 2020; Tsabouri *et al.*, 2021). Persistent wheeze was defined as any two reports of wheeze. Eczema/atopic dermatitis was defined as any physician-diagnosed eczema or atopic dermatitis at 8, 12, 18, 24, 30 and 36 months of age. Allergies (grouped reported food, medicine, dust, animal, pollen and ragweed allergies) were defined as any physician-diagnosed allergy at 8, 12, 18, 24, 30 and 36 months of age. Information on medications

prescribed for atopic outcomes was not collected in infancy. Although any report of physician-diagnosed asthma was collected at 18, 24, 30, and 36 months of age, incidence was rare (n = 123; 2.1%) so we did not examine asthma in this age group.

Middle childhood atopic outcomes evaluated at approximately 7, 8, or 9 years of age included asthma, eczema/atopic dermatitis, allergies, and lung inflammation. Mothers completed questionnaires annually between 2016 and 2019. Asthma was defined as any maternal report of current physician-diagnosed asthma or prescription of asthma medication/inhaler in the past year. Eczema/atopic dermatitis was defined as any report of physician-diagnosed eczema or atopic dermatitis. Allergies were defined as any report of seeing a doctor for allergy or allergy medication use in the past year. A study visit was conducted among a subgroup of children (n = 373) when they were 8–11 years old (median: 9). Eosinophilic airway inflammation was measured by fractional exhaled nitric oxide (FeNO), a biomarker commonly used to diagnose and characterize atopic conditions (Dweik *et al.*, 2011). FeNO was measured in parts per billion (ppb) using a NIOX® device (Circassia Limited, Morrisville, NC, USA), with values below 5 ppb set to 5 ppb.

Covariates

Covariate information was collected via vital records (maternal and paternal ages at delivery, insurance status, plurality, previous live birth, pre-pregnancy BMI (calculated as weight in kilograms divided by height in meters squared) or baseline maternal report at approximately 4 months postpartum (paternal weight and height, race/ethnicity, marital status, education, smoking during pregnancy, and maternal and paternal asthma and atopy)).

Statistical analysis

Sociodemographic and clinical characteristics by infertility treatment were compared using Chi-square and Student's *t*-tests. These baseline comparisons were made at the family level (n = 4912) so as to not double count information from families with twins. Analyses excluded higher order multiples (triplets and quadruplets, n = 134) due to small numbers. Figure 1 shows participant exclusion and data availability for the outcomes defined above; including infant atopy (n = 5939), infant persistent wheeze (n = 5012), and childhood asthma/atopy (n = 2056) analytic samples.

Poisson regression with robust standard errors were used to estimate the relative risk (RR) and 95% CI for the association between infertility treatment and atopic outcomes (Zou and Donner, 2013). Linear regression estimated the β (95% CI) for the association between infertility treatment and pulmonary inflammation. To account for the potential lack of independence between twins of the same family, models included a random effect for maternal ID. Models provided comparisons by infertility treatment [any versus none (reference)] and then treatment type [ART, ovulation induction via oral/injectable medications with or without IUI (OI/IUI), none (reference)]. Analyses were run unadjusted and adjusted for maternal and paternal ages, insurance status, plurality, previous live birth, maternal and paternal BMI, maternal race/ethnicity, marital status, education, smoking during pregnancy, and maternal and paternal asthma and atopy.

To account for oversampling on infertility treatment and twins, infant and middle childhood models were run with sampling weights based on infertility treatment, plurality, and region of birth of all live births in New York State during the recruitment period (Buck Louis *et al.*, 2014). Sampling weights were trimmed at the 95th percentile for the infant outcomes analyses. To account for missing outcome data in middle childhood, inverse probability treatment weights were derived from multivariate logistic regression models (Perkins *et al.*, 2018). Sampling and inverse probability treatment weights were multiplied and then trimmed at the 95th percentile for middle childhood analyses. Fifty datasets were created using multiple imputation by chained equations to account for missing covariate data. The covariates imputed and numbers of participants missing them are reported in Table I (footnotes).

A few sensitivity analyses were conducted. First, there is some evidence that these effects differ by plurality, with only singletons exhibiting a higher risk of asthma following ART (Magnus *et al.*, 2019; Tsabouri *et al.*, 2021). Thus, we examined our associations with stratification by plurality. Second, given that pulmonary inflammation obtained from FeNO may be lower among children correctly medicated for their asthma or atopy (Wang *et al.*, 2020), we re-ran this analysis among children who did not have asthma or allergy medications reported on the childhood questionnaires. Lastly, we examined effect estimates based on applying sampling weights or inverse probability treatment weights only among the middle childhood outcomes. All analyses were performed using SAS version 9.4 (SAS Institute Inc., NC, USA).

Results

Table I shows sociodemographic and clinical characteristics of the study participants by infertility treatment status. Mothers of children who received infertility treatment were more likely to be of older age, nulliparous, non-Hispanic White, married or cohabitating, of higher socioeconomic status (e.g. college educated, private insurance status), report atopic conditions and less likely to smoke during pregnancy compared to women who did not undergo infertility treatment or between the two treatment types (ART or OI/IUI). Further, maternal and paternal BMI was higher, and atopy was more common, among those who underwent OI/IUI.

By 36 months, 10.8%, 28.2%, and 8.8% of children were reported to have persistent wheeze, eczema/atopic dermatitis, or allergies (including food), respectively. By middle childhood, 16.4% were classified as having current asthma (physician diagnosis or medication in past year), 10.4% with eczema, 14.1% with physician diagnosed allergies and 13.4% were prescribed allergy medications by a physician. Among those with persistent wheeze by age 3 years, 46.6% reported current asthma in middle childhood (50.5% male, 40.9% female).

Table II presents the associations of any infertility treatment (ART or OI/IUI) and atopy outcomes in early and late childhood. Beginning with outcomes occurring up to 36 months of age, the risk of persistent wheeze was higher among infants conceived with, compared to without, infertility treatment (adjusted RR: 1.55; 95% CI: 1.11, 2.17). A borderline association for any atopy (aRR: 1.12; 95% CI: 0.98, 1.28) was observed but not for eczema/atopic dermatitis or food allergies. At 7–9 years old, children conceived with any infertility treatment were at an increased risk of asthma (aRR: 1.27; 0.96, 1.68), driven by physician diagnosed cases (aRR: 1.56; 95% CI: 1.01, 2.40). Any atopy (aRR:

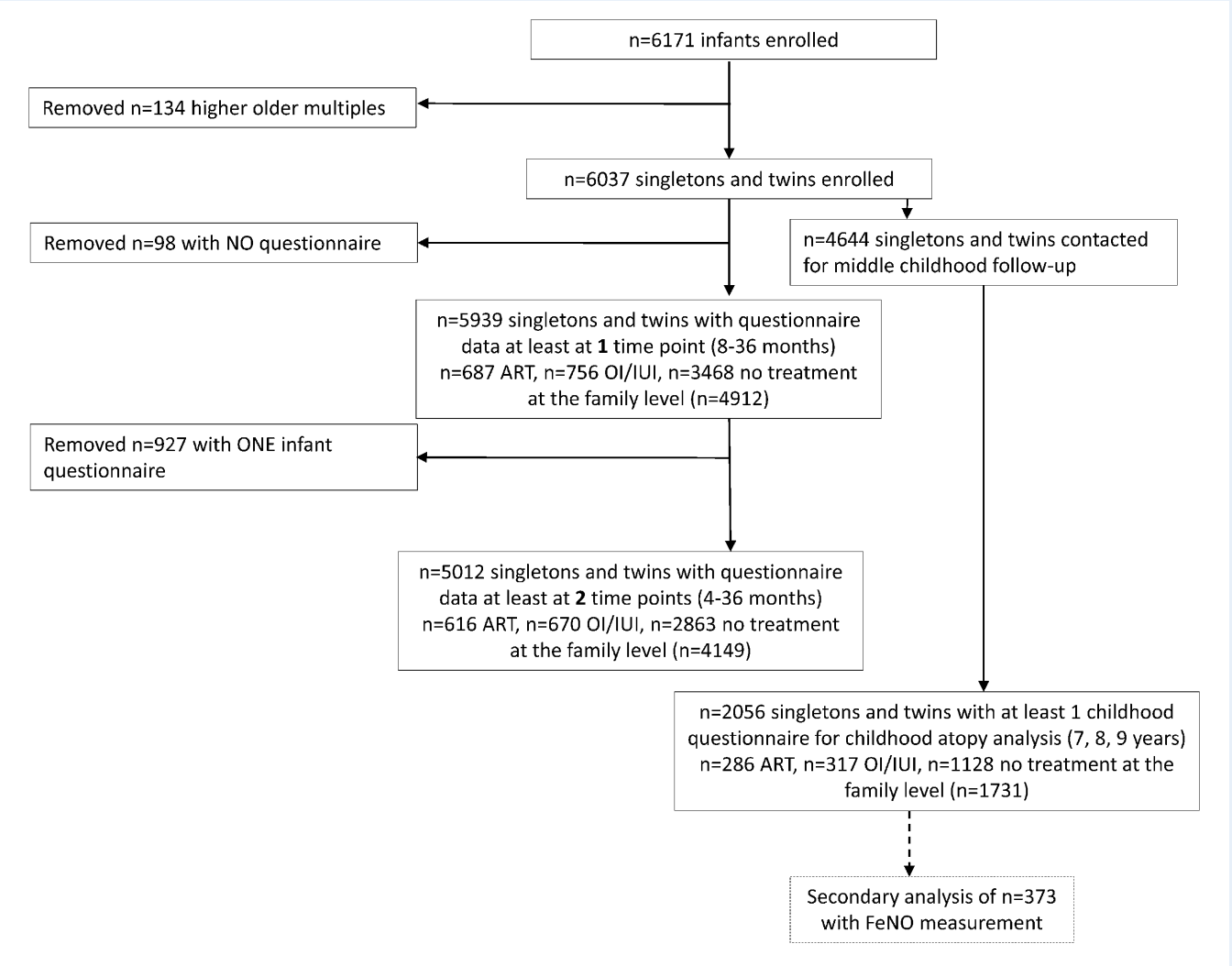

Figure 1. Flow chart of study sample for primary and secondary analyses of outcomes in infancy and middle childhood, Upstate KIDS Study, USA (2008–2019). FeNO: by fractional exhaled nitric oxide; OU, ovulation induction.

1.52; 95% CI: 1.20, 1.92), including eczema risk (aRR: 1.69; 95% CI: 1.19, 2.39) was also increased among those conceived with any infertility treatment. Of note, similar effect estimates were found when excluding maternal and paternal asthma and atopy from the models (data not shown). In sensitivity analyses repeating our analysis in singletons and twins separately, we found only singletons exhibiting a higher risk of persistent wheeze or atopic conditions in childhood (Supplementary Table SI). The risk for childhood atopy, particularly eczema, was increased in twins though not statistically significant. In addition, Supplementary Fig. S1 presents results of sensitivity analyses for effect estimates based on the use of imputation and sampling weights for our childhood outcomes. The magnitude of the effect was similar across weighting and imputation methods, though statistical significance varied.

We then examined whether associations differed by type of infertility treatment (Table III). In early childhood, the risk of persistent wheeze was increased in infants conceived via OI/IUI compared to no infertility treatment (aRR: 1.69; 95% CI: 1.14, 2.51). No associations were observed with eczema/atopic dermatitis and food-related allergies by 36 months of age after accounting for covariates. In older childhood, there was an increased risk of physician diagnosed asthma (aRR: 1.65; 95% CI: 1.04, 2.62) among those conceived by OI/IUI compared to no treatment. Positive associations of OI/IUI with eczema (aRR: 1.91; 95% CI: 1.32, 2.78) and with physician-prescribed allergy medications (aRR: 1.45; 95% CI: 1.04, 2.02) were found after covariate adjustment. Similar effect sizes for eczema (aRR: 1.45; 95% CI: 0.92, 2.28) and physician-prescribed allergy medications (aRR: 1.46; 95% CI: 0.97, 2.19) were observed among those conceived by ART, though with low precision.

Table IV presents the associations of infertility and pulmonary inflammation obtained from FeNO measurements in middle childhood. Average FeNO measurements were 12.93 (SD: 12.5) ppb in children who were conceived without infertility and 13.49 (SD 13.14) among children conceived with any type of fertility treatment. For reference, values below 20 ppb are considered 'low' (Dweik *et al.*, 2011). Infertility treatment or infertility treatment type were not significantly associated with FeNO levels. Inferences were similar after limiting

Table 1 Baseline characteristics (n (%) or mean ± SD) associated with infertility treatment, Upstate KIDS Study, USA (2008–2019).

	No treatment	Infertility treatment		
	n = 3468	Any (ART or OI/IUI) n = 1444	ART n = 756	OI/IUI n = 687
Age (years)				
Maternal[a,b,c]	28.96 ± 5.77	34.09 ± 5.14	35.76 ± 5.20	32.58 ± 4.59
Paternal[a,b,c]	31.71 ± 6.58	36.36 ± 6.30	38.09 ± 6.33	34.77 ± 5.84
Previous live birth[a,b,c]				
Yes	2101 (60.58)	593 (41.07)	286 (41.63)	306 (40.48)
No	1367 (39.42)	851 (58.93)	401 (58.37)	450 (59.52)
Maternal race/ethnicity[a,b,c]				
Non-Hispanic White	2695 (77.71)	1254 (86.84)	578 (84.13)	676 (89.42)
Other race/ethnicity[d]	773 (22.29)	190 (13.16)	109 (15.87)	80 (10.58)
Marital status[a,b,c]				
Married/living as married	2836 (85.34)	1325 (95.32)	631 (95.75)	694 (94.94)
Single/widowed/other	487 (14.66)	65 (4.68)	28 (4.25)	37 (5.06)
Education[a,b,c]				
<College education	2035 (58.68)	389 (26.94)	156 (22.71)	233 (30.82)
≥College education	1433 (41.32)	1055 (73.06)	531 (77.29)	523 (69.18)
Insurance status[a,b,c]				
Private insurance	2309 (66.64)	1370 (94.94)	662 (96.36)	708 (93.77)
Other	1156 (33.36)	73 (5.06)	25 (3.64)	47 (6.23)
Maternal smoking during pregnancy[a,b,c]				
No	2831 (81.66)	1386 (96.05)	662 (96.5)	723 (95.63)
Yes	636 (18.34)	57 (3.95)	24 (3.5)	33 (4.37)
Pre-pregnancy BMI (kg/m^2)				
Maternal[b,c]	27.00 ± 6.82	27.29 ± 6.87	26.23 ± 5.99	28.25 ± 7.46
Paternal[a,b,c]	27.96 ± 5.45	28.87 ± 5.39	28.43 ± 5.00	29.27 ± 5.70
Asthma				
Maternal asthma[b]	548 (16.26)	223 (15.78)	94 (14.07)	129 (17.32)
No maternal asthma	2823 (83.74)	1190 (84.22)	574 (85.93)	616 (82.68)
Paternal asthma	368 (10.92)	130 (9.2)	67 (10.03)	63 (8.46)
No paternal asthma	3003 (89.08)	1283 (90.8)	601 (89.97)	682 (91.54)
Atopy				
Maternal atopy[a,c]	1101 (32.66)	530 (37.51)	249 (37.28)	281 (37.72)
No maternal atopy	2270 (67.34)	883 (62.49)	419 (62.72)	464 (62.28)
Paternal atopy[c]	805 (23.88)	371 (26.26)	185 (27.69)	186 (24.97)
No paternal atopy	2566 (76.12)	1042 (73.74)	483 (72.31)	559 (75.03)
Plurality[a,b,c]				
Singleton	2820 (81.31)	1015 (70.29)	455 (66.23)	559 (73.94)
Multiple	648 (18.69)	429 (29.71)	232 (33.77)	197 (26.06)

[a]*P*-value <0.05 in comparison between infertility treatment to no treatment.
[b]*P*-value <0.05 in comparison between ART to no treatment.
[c]*P*-value <0.05 in comparison between OI/IUI to no treatment.
[d]Other race/ethnicity includes: non-Hispanic Black (4.9%); non-Hispanic Asian (2.7%); Hispanic (5.9%); Multiracial or other race (6.2%).
Missing information: maternal smoking (n = 2), insurance status (n = 4), parental asthma (n = 128), pre-pregnancy BMI (n = 10), parental atopy (n = 128), marital status (n = 199), paternal age (n = 344), paternal BMI (n = 535).
OI/IUI, ovulation induction via oral/injectable medications with or without IUI.

Table II Association between infertility treatment (ART or OI/IUI versus none) and asthma and other atopic outcomes, Upstate KIDS Study, USA (2008–2019).

	n (%)[a]		RR (95% CI)	
	No infertility treatment (ref)	Infertility treatment	Unadjusted	Adjusted[b]
Infant outcomes (4–36 months)				
Persistent wheeze	357 (10.62)	186 (11.27)	**1.47 (1.08, 2.01)**	**1.55 (1.11, 2.17)**
Any atopy	1488 (36.46)	840 (45.21)	**1.24 (1.09, 1.40)**	1.12 (0.98, 1.28)
Eczema/atopic dermatitis	1060 (25.97)	618 (33.26)	**1.23 (1.04, 1.44)**	1.06 (0.88, 1.27)
Food allergies	325 (9.43)	200 (11.96)	1.09 (0.78, 1.52)	1.04 (0.72, 1.50)
Childhood outcomes (7–9 years)				
Any asthma	212 (16.33)	126 (16.67)	1.01 (0.80, 1.26)	1.27 (0.96, 1.68)
Physician-diagnosed	92 (7.14)	56 (7.44)	1.03 (0.73, 1.47)	**1.56 (1.01, 2.40)**
Medications	200 (15.53)	122 (16.20)	1.06 (0.84, 1.34)	1.26 (0.95, 1.69)
Any atopy	263 (20.25)	187 (24.74)	1.14 (0.95, 1.37)	**1.52 (1.20, 1.92)**
Eczema	118 (9.14)	95 (12.60)	**1.36 (1.02, 1.82)**	**1.69 (1.19, 2.39)**
Allergies				
Physician-diagnosed	173 (13.42)	117 (15.54)	1.22 (0.96, 1.57)	1.10 (0.82, 1.49)
Medications	159 (15.50)	117 (18.54)	1.06 (0.83, 1.35)	**1.46 (1.07, 1.99)**

[a]n (%) are based on 5012 children for persistent wheeze, 5939 children for other infant outcomes, and 2056 children for childhood outcomes. Covariate data are imputed. Bold indicates statistical significance.
[b]Model is adjusted for maternal and paternal ages, insurance status, plurality, previous live birth, maternal and paternal BMI, maternal race/ethnicity, marital status, education, smoking during pregnancy, and parental asthma and atopy.
OI/IUI, ovulation induction via oral/injectable medications with or without IUI; ref, reference; RR, relative risk.

Table III Association between infertility treatment type and asthma and other atopic outcomes, Upstate KIDS Study, USA (2008–2019).

	ART			OI/IUI		
	n (%)[a]	RR (95% CI)		n (%)[a]	RR (95% CI)	
		Unadjusted	Adjusted[b]		Unadjusted	Adjusted[b]
Infant outcomes (4–36 months)						
Persistent wheeze	92 (11.25)	1.17 (0.76, 1.81)	1.29 (0.81, 2.04)	94 (11.30)	**1.67 (1.13, 2.46)**	**1.69 (1.14, 2.51)**
Any atopy	409 (44.85)	**1.21 (1.03, 1.43)**	1.06 (0.88, 1.28)	431 (45.61)	**1.25 (1.07, 1.47)**	1.16 (0.98, 1.36)
Eczema/atopic dermatitis	296 (32.46)	**1.26 (1.01, 1.56)**	1.03 (0.80, 1.32)	322 (34.07)	1.21 (0.98, 1.50)	1.07 (0.86, 1.34)
Food allergies	104 (12.53)	1.18 (0.77, 1.79)	1.13 (0.71, 1.82)	96 (11.41)	1.03 (0.64, 1.66)	0.99 (0.61, 1.60)
Childhood outcomes (7–9 years)						
Any asthma	61 (16.27)	0.98 (0.73, 1.32)	1.27 (0.88, 1.82)	65 (17.06)	1.04 (0.79, 1.36)	1.27 (0.94, 1.72)
Physician-diagnosed	25 (6.68)	0.93 (0.58, 1.48)	1.46 (0.83, 2.57)	31 (8.18)	1.15 (0.76, 1.74)	**1.65 (1.04, 2.62)**
Medications	59 (15.82)	1.04 (0.77, 1.41)	1.24 (0.85, 1.81)	63 (16.58)	1.09 (0.82, 1.45)	1.28 (0.94, 1.75)
Any atopy	87 (23.20)	1.07 (0.84, 1.35)	**1.48 (1.09, 2.00)**	100 (26.25)	1.23 (0.98, 1.54)	**1.56 (1.22, 2.00)**
Eczema	42 (11.23)	1.14 (0.79, 1.64)	1.45 (0.92, 2.28)	53 (13.95)	**1.61 (1.14, 2.28)**	**1.91 (1.32, 2.78)**
Allergies						
Physician-diagnosed	49 (15.86)	1.04 (0.75, 1.43)	0.92 (0.62, 1.37)	68 (21.12)	**1.42 (1.07, 1.90)**	1.30 (0.95, 1.78)
Medications	55 (14.75)	1.02 (0.75, 1.40)	1.46 (0.97, 2.19)	62 (16.32)	1.10 (0.82, 1.48)	**1.45 (1.04, 2.02)**

Reference category for analyses is no infertility treatment.
[a]n (%) are based on 5012 children for persistent wheeze, 5939 children for other infant outcomes, and 2056 children for childhood outcomes. Covariate data are imputed. Bold indicates statistical significance.
[b]Model is adjusted for maternal and paternal ages, insurance status, plurality, previous live birth, maternal and paternal BMI, maternal race/ethnicity, marital status, education, smoking during pregnancy, and parental asthma and atopy.
OI/IUI; ovulation induction via oral/injectable medications with or without IUI; RR, relative risk.

Table IV Association between infertility treatment and childhood pulmonary inflammation assessed by FeNO measurements, Upstate KIDS Study, USA (2008–2019).

	No infertility treatment	Infertility treatment		
	n = 204	Any n = 169	ART n = 82	OI/IUI n = 87
FeNO Mean ppb (SD)	12.93 (12.50)	13.49 (13.14)	14.80 (14.54)	12.25 (11.61)
β (95% CI)				
Unadjusted	Ref.	1.08 (−2.33, 4.49)	2.47 (−2.07, 7.02)	−0.42 (−4.28, 3.44)
Adjusted[a]	Ref.	3.10 (−0.84, 7.03)	4.16 (−0.93, 9.24)	2.06 (−2.37, 6.48)

[a]Model is adjusted for maternal and paternal ages, insurance status, plurality, previous live birth, maternal and paternal BMI, maternal race/ethnicity, marital status, education, smoking during pregnancy, and parental asthma and atopy.
FeNO, fractional exhaled nitric oxide; OI/IUI, ovulation induction via oral/injectable medications with or without IUI; ppb, parts per billion; Ref., reference.

analysis to children who did not report being prescribed asthma or respiratory allergy medications in the past year during the clinic visit when the FeNO measurements were obtained (Supplementary Table SII).

Discussion

Our analyses support evidence of an association between infertility treatment and atopic conditions in childhood. Compared to children conceived without treatment, children conceived with any infertility treatment were at an increased risk of persistent wheeze by age 3 years. Further, in middle childhood, these children are more likely to have asthma, eczema or be prescribed allergy-related medications. Similar effect sizes, albeit with differing precision, were found when examining associations by treatment type (ART or OI/IUI) indicating underlying parental subfertility or shared ovarian stimulation protocols may be contributing to risk, rather than specific techniques used. These associations persisted after concurrent adjustment for maternal and paternal asthma or atopy. Given some differences in strength of associations when defining outcomes based on physician diagnosis compared to reported use of medications, we cannot rule out the possibility that parents who actively sought infertility treatment may also be more likely to seek medical care for their child (Carson *et al.*, 2013). On the other hand, medication use might have captured use in treating respiratory illnesses that did not concord with an asthma diagnosis.

Comparison with previous studies

Our findings are largely consistent with the positive associations of infertility treatment (and/or parental subfertility) and asthma reported in many previous studies (Klemetti *et al.*, 2010; Finnström *et al.*, 2011; Carson *et al.*, 2013; Källén *et al.*, 2013; Halliday *et al.*, 2014, 2019; Kuiper *et al.*, 2015; Magnus *et al.*, 2019; Tsabouri *et al.*, 2021), but not all (Kuiper *et al.*, 2019). Only one prior study examining IVF and childhood asthma has been conducted in a US population (Sicignano *et al.*, 2010). This cross-sectional study did not find an association between treatment and childhood asthma. Few prior studies have examined the association between specific types of infertility treatment, such as OI/IUI, and childhood asthma. A recent meta-analysis of the three studies that have examined this association reported an increased odds ratio (OR: 1.34; 95% CI: 1.17, 1.54) (Tsabouri *et al.*, 2021). That we found evidence that both OI and ART elevated asthma risk suggests either the use of common ovulation protocols playing a role, or underlying infertility. Few prior studies have included and examined multiple births. In examining singletons and twins separately, a Finnish register-based study observed statistically significant increased odds of asthma and allergy by age 4 years in singletons, and non-significant associations in multiples conceived by non-ART infertility treatment (Klemetti *et al.*, 2010).

This study greatly adds to the existing literature examining infertility treatment and atopic conditions beyond asthma. Children who were conceived with infertility treatment had increased risks of any atopy (respiratory, skin) and were more likely to be prescribed medications for allergies during middle childhood. These findings are in line with the higher prevalence of maternally reported hospitalization for any atopy (respiratory, skin and food-related) within the first 18 years of the child's life in an Australian-based cohort comparing ART and non-ART births (Halliday *et al.*, 2014) and a recent study utilizing skin prick tests to examine allergy sensitization to foods and aeroallergens among children conceived with or without any type of infertility treatment (Schäfer *et al.*, 2020). However, they are in contrast to findings from the UK Millennium Cohort, which found no increase in atopic conditions (hay fever and eczema) among children conceived via ART (Carson *et al.*, 2013). Similar to our findings within singletons, a Finnish register-based study investigating OI with a number of childhood outcomes by age 4 years found a weak positive association of any allergy in singletons (OR: 1.21; 95% CI: 1.00, 1.47) (Klemetti *et al.*, 2010). In multiples, the increased risk of allergy persisted but was not statistically significant (OR: 1.55, 95% CI: 0.63, 3.85) (Klemetti *et al.*, 2010). We did not find support for differences in food allergy up to age 3 years by treatment group, which is consistent with an earlier study in which any infertility treatment was not associated with food allergen sensitization among 5-year-old children (Hsu *et al.*, 2013).

The clinical assessment of airway inflammation via FeNO did not reveal differences by treatment group in middle childhood. Average FeNO values in our study population were 'low' (i.e. <20 ppb), which implies noneosinophilic or no airway inflammation in children (Dweik *et al.*, 2011). Therefore, we cannot rule out other mechanisms such as neutrophilic airway inflammation (Carr *et al.*, 2018). To our knowledge

no other studies have compared FeNO measures in children conceived with and without infertility treatments. One prior cohort has reported measures of lung function (forced expiratory volume and forced vital capacity at age 22 years); they did not find differences in lung function by ART status (Halliday et al., 2019). FeNO has been weakly associated with lung function (Lo et al., 2019).

Potential biologic mechanisms

More studies exploring the underlying biological mechanisms of infertility treatment on asthma/atopic conditions in the offspring are needed. Previous studies have suggested that medications taken to induce ovulation or ART procedures may impact development (Vannuccini et al., 2016); however, a specific mechanism linking treatment to asthma/atopic conditions in offspring has yet to be confirmed. Conflicting evidence has suggested infertility is more common among women with asthma and other atopic diseases (Juul Gade et al., 2014; Bláfoss et al., 2019; Wasilewska and Małgorzewicz, 2019). This observation was to some extent supported in our study as women who received any infertility treatment were more likely to also report atopic conditions, but not asthma. Further, certain pregnancy complications, such as preeclampsia, preterm delivery, low birthweight, or cesarean delivery, are more common in pregnancies conceived with infertility treatment (Qin et al., 2016) and have been associated with the development of asthma or atopy in children (Been et al., 2014; Mebrahtu et al., 2015; Keag et al., 2018). However, a formal mediation analysis did not find that these factors mediated the association between subfertility and childhood atopic outcomes (Magnus et al., 2019), and studies with additional adjustment for these factors do not report substantial attenuation of effects (Carson et al., 2013). Thus, it appears that other factors likely account for this association. Other lines of research implicate *in utero* exposure to maternal asthma or atopic conditions with the development of immune responses in the child (Barrett, 2008). We continued to observe associations between infertility treatment and childhood atopic outcomes, even after adjustment for both paternal and maternal asthma and atopy, suggesting independent effects for infertility treatment on offspring asthma/allergy risk. It therefore appears that the inheritance of, *in utero* exposure to, and/or treatment of parental asthma or atopy do not fully explain the observed association between infertility treatment and atopic outcomes. Future studies are needed to tease apart the effects of infertility treatment from the effects of subfertility on these outcomes.

Strengths and limitations

The strengths of the current study include the recruitment and long-term follow up of children conceived with and without infertility treatment as well as twins from a population-based source, the use of prospectively collected data on atopic conditions, and the collection of important covariates including pre-pregnancy parental asthma and atopy. Limitations of the study include potential misclassification of childhood atopic outcomes based on maternal report. In particular, the outcome definition of eczema in the middle childhood follow-up questionnaires was based on the questionnaire wording 'Eczema or any kind of skin allergy (like contact dermatitis)'. Contact dermatitis is not an allergic reaction and is less common in early childhood; in contrast, atopic dermatitis is caused by an allergic reaction and most commonly develops in children aged 5 years or younger (Thomsen, 2014). However, based on the reported prevalence in this study, eczema was less common in later childhood (10.4%) compared to by early childhood (28.2%), as would be expected. Second, we did not examine potential mediation by pregnancy complications (e.g. birthweight, cesarean delivery) as a formal mediation analysis was beyond the scope of this manuscript, and additional adjustment for potential mediators can lead to biased estimates (Cole et al., 2010; Wang et al., 2017). Further it is possible that children conceived with infertility treatment may be more likely to receive diagnoses for these conditions because their parents may represent a group that more actively seeks medical care and/or is in a higher socioeconomic position to receive care. Lastly, the clinical relevance of our findings may also be limited in precision due to attrition. Nevertheless, we accounted for attrition using inverse-probability weights.

Conclusion

Overall, our longitudinal study provides evidence supporting an elevated risk of asthma/atopic conditions among children conceived with infertility treatment. These associations between infertility treatment and asthma/allergy persisted even after adjustment for parental asthma and atopy. Our findings of similar effect sizes by infertility treatment type suggest either shared biological process of inducing ovulation leading to fetal exposure to supraphysiological hormone levels or underlying parental subfertility may contribute to risk. Future research is needed to elucidate the mechanisms of infertility treatment on childhood atopic conditions, including separating treatment effects from the effects of parental subfertility.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Authors' roles

All authors contributed substantially to the paper via conceptualization (K.J.P., D.R.S. and P.M.), methodology (K.J.P., D.R.S., P.M., T.-C.L., R.S., E.B. and E.H.Y.), software (K.J.P., D.R.S. and T.-C.L.), validation (T.-C.L., R.S. and E.H.Y.), formal analysis (K.J.P. and T.-C.L.), investigation (K.J.P., D.R.S., P.M., T.-C.L., R.S., E.B. and E.H.Y.), resources (E.H.Y.), data curation (K.J.P., D.R.S., T.-C.L., R.S. and E.H.Y.), writing—original draft (K.J.P., D.R.S., P.M. and E.H.Y.), writing—review & editing (K.J.P., D.R.S., P.M., T.-C.L., R.S., E.B. and E.H.Y.), visualization (K.J.P., D.R.S. and T.-C.L.), supervision (P.M., E.B. and E.H.Y.), project administration (P.M., E.B. and E.H.Y.), and funding acquisition (E.B. and E.H.Y.).

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Conflict of interest

The authors have no relevant conflicts of interest to disclose.

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